UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,175	03/01/2002	Bryon E. Petersen	A32212-PCT USA	1973

21003 7590 02/25/2004

BAKER & BOTTS
30 ROCKEFELLER PLAZA
NEW YORK, NY 10112

EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/914,175	PETERSEN ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 20-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/24/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-24 are pending in the present application.

Applicant's election of Group III (claims 15-19) in the Response to Restriction Requirement dated 11/10/03 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-14 and 20-24 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 15-19 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the

predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a method for stimulating pancreatic regeneration in a subject having a pancreatic disorder comprising administering of bone marrow cells to said subject in an amount sufficient to result in the production of pancreatic cells (claim 15); the same method wherein the bone marrow cells are injected (claim 16); the same method wherein the bone marrow cells are transplanted into the pancreas (claim 17); the same method wherein the bone marrow cells are genetically engineered to express a functionally active protein (claim 18); and the same method wherein the bone marrow cells are on a support matrix (claim 19).

With respect to the nature of the present elected invention, the instant specification teaches by exemplification showing that when bone marrow cells from DPPIV+ F-344 male rats were injected into lethally irradiated DPPIV- F-344 females, the transplanted bone marrow cells were capable of infiltrating and incorporating into pancreas as evidenced by the detection of a few reddish/burn orange cells staining positive for DPPIV in the recipient pancreas 60 days post bone marrow transplantation (see Figure 17-A-F; page 9, lines 10-20). The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the presently claimed invention.

When read in light of the specification, the sole purpose for the presently claimed invention is to attain therapeutic effects (e.g., development of a new pancreatic tissue,

restoration of pancreatic function, alleviating the symptoms associated with pancreatic disorders) for a subject having a pancreatic disorder such as acute or chronic pancreatitis or carcinomas of the pancreas (see section titled "Use of bone marrow cells for regeneration of tissue other than liver tissue" on pages 17-18) through the administration of bone marrow cells into said subject. The instant specification is not enabled for presently claimed invention for the following reasons.

(1) The breadth of the claims. The claims are drawn to a method of stimulating pancreatic regeneration in a subject having any pancreatic disorder comprising administering bone marrow cells derived from any source to said subject by any route of delivery in an amount sufficient to result in the production of any pancreatic cells. With respect to claim 18, the bone marrow cells are genetically engineered to express any functionally active proteins such as growth factors, cytokines, hormones, inhibitors of cytokines, peptide growth and differentiation factors.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application (2/26/1999), nothing was known on the capability of any bone marrow cell population that stimulates pancreatic regeneration in any subject having a pancreatic disorder. Particularly, nothing was known on the ability of any bone marrow cell population to differentiate and/or proliferate into various pancreatic cell types such as acinar cells, β-(insulin producing), α-(glucagons producing), δ-(somatostatin containing) and PP (pancreatic polypeptide) cells into sufficient numbers to generate a functional new pancreatic tissue to yield the therapeutic effects contemplated by Applicants. Even 4 years after the effective filing date of the present application the

issue "stem cell plasticity", the ability of cell types from adult tissues to take on surprising new identities (for this instance the ability of transplanted bone marrow cells to produce sufficient pancreatic cells to stimulate pancreatic regeneration in a subject having a pancreatic disorder) remains controversial (Holden et al., Science 296:2126-2129, 2002). Wagers et al. (Science 297:2256-2259, 2002) demonstrated that there is little evidence for developmental plasticity of adult hematopoietic stem cells.

Furthermore, with respect to claim 18, at about the effective filing date of the present application (2/26/1999) the attainment of any therapeutic effects via gene therapy (including *in vivo* and/or *ex vivo* gene therapy) in general remains unpredictable as evidenced by the teachings Dang et al. (Clin. Cancer Res. 5:471-474, 1999) and Romano et al. (Stem Cells 18:19-39, 2000). Several factors that are known to limit an effective gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors or genetically modified cells, particularly those derived from any source including autologous, allogeneic as well as xenogeneic genetically modified bone marrow cells.

(3) The amount of direction or guidance provided. Apart from the exemplification showing that transplanted bone marrow cells from DPPIV+ F-344 male rats were capable of infiltrating and incorporating into pancreas of DDPIV- F-344 female rats as evidenced by the detection of a few reddish/burn orange cells staining positive for DPPIV in the recipient pancreas 60 days post bone marrow transplantation (see Figure 17-A-F; page 9, lines 10-20), the instant specification fails to provide sufficient guidance

for a skilled artisan in the art on how to attain any therapeutic effects (e.g., development of a new pancreatic tissue, restoration of pancreatic function, alleviating the symptoms associated with pancreatic disorders) contemplated by Applicants for the methods as claimed. The detection of a few reddish/burn orange cells staining positive for DPPIV in DPPIV- recipient pancreas is not reasonably correlated with any of the desired therapeutic effects. This is because there is no evidence of record indicating or suggesting that the detected cells staining positive for DPPIV are capable of differentiating or proliferating into any pancreatic cell types in sufficient numbers to yield any therapeutic effects for a subject having a pancreatic disorder. Nor is there any evidence indicating or suggesting the detected cells staining positive for DPPIV are capable of resulting in the production of sufficient number of pancreatic cells in any mysterious manner to yield the desired therapeutic effects in a subject having a pancreatic disorder. Since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present application to do so. Given the lack of sufficient guidance provided by the present application, coupled with the state and the unpredictability of the relevant art discussed above, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

With respect to claim 18, the instant specification also fails to provide sufficient guidance for a skilled artisan on any specific construct encoding a functionally active protein for genetically modifying the transplanted bone marrow cells, the dosage and the route of administering the genetically modified cells into a subject having a

pancreatic disorder to yield the desired therapeutic effects. On the basis of the instant disclosure, it is unclear whether any effective level of any functionally active protein could be generated by the transplanted bone marrow cells in a subject having a pancreatic disorder to yield the desired therapeutic effects. It is well known in the gene therapy art that level of transgene expression *in vivo*, its duration, and its *in vivo* therapeutic effects sought for are unpredictable. Therefore, in light of the state of the relevant art at the effective filing date of the present application as already mentioned above, coupled with the lack of sufficient guidance provided by the present disclosure, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

The instant claims also encompass the use of any bone marrow cells derived from autologous, allogeneic as well as xenogeneic donors. It is also well known in the art that transplanting any tissues or cells that are not antigenically matched would result in strong and adverse host immune responses against the transplanted cells or tissues. As such, then how could bone marrow cells from a xenogeneic donor survive in a treated subject for a sufficient period of time to yield any of the therapeutic effects contemplated by Applicants? Once again, with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

The instant broad claims (claims 15-16 and 18-19) encompass any route of delivering bone marrow cells into a subject having a pancreatic disorder (e.g., injections at any site or tissue in the subject). However, there is no evidence of record indicating

or suggesting that subcutaneous or intramuscular injections of bone marrow cells or implanting bone marrow cells at tissues other than the pancreas in the treated subject, for examples, would result in the production of pancreatic cells in sufficient numbers to yield any of the desired therapeutic effects. Once again, since the prior art at the effective filing date of the present application does not provide such guidance, it is incumbent upon the present specification to do so. Otherwise, with the lack of sufficient guidance provided by this disclosure, it would have required undue experimentation for a skilled artisan to make and use the methods as claimed.

(4) Working example provided. There is no *in vitro* and/or *in vivo* example pertaining to capability of any transplanted bone marrow cell population to differentiate and proliferate into any pancreatic cell types or result in the production of pancreatic cells by a mysterious mechanism in sufficient numbers to yield any of the therapeutic effects contemplated by Applicants (e.g., development of a new pancreatic tissue, restoration of pancreatic function, alleviating the symptoms associated with pancreatic disorders).

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the unpredictability of the art on pancreatic regeneration in a subject having a pancreatic disorder using bone marrow cells' transplantation and ex vivo gene therapy art, it would have required undue experimentation for one skilled in the art to make and use the instant claimed invention.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.

DAVID GUZO
PRIMARY EXAMINER